1. PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Jun MORI et al.

Application No.: 10/533,534

Filed: June 22, 2005

Group Art Unit: 1618

Examiner: M. Young

Docket No.: 123680

For: PERCUTENOUS ABSORPTION PREPARATION CONTAINING 3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE

**DECLARATION UNDER 37 C.F.R. §1.132**

I, Jun MORI, a citizen of Japan, hereby declare and state:

1. I have a bachelor's degree in pharmacy which was conferred upon me by Toyama Medical and Pharmaceutical University in Toyama, Japan, in 1988, and a doctor's degree in pharmacy which was conferred upon me by University of Toyama in Toyama, Japan, in 2006.

2. I have been employed by Lead Chemical Co., Ltd. since 1995 and I have had a total of 15 years of work and research experience in pharmacology and pharmaceutics.

3. I am a named inventor in the above-captioned patent application.

4. I and/or those under my direct supervision and control have conducted the following tests, and/or have acquired knowledge about adhesive preparation through studying the relevant scientific literature, in support of U.S. Patent Application No. 10/533,534:

(1) Preparation of Percutaneous Absorption Preparations

(1)-(a) Present Invention

According to the procedure of Example 1 of the specification, a mixture for a percutaneous absorption adhesive preparation to be tested according to the claimed invention

was prepared. That is, a percutaneous absorption preparation of the claimed invention was prepared as follows:

Liquid A was adjusted by mixing 5 parts of sodium polyacrylate, 6 parts of starch acrylate, 12 parts of talc and 29.1 parts of concentrated glycerin. Liquid B was adjusted by dissolving 2.3 parts of tartaric acid in 30 parts of water. Liquid C was adjusted by dissolving 3 parts of 3-methyl-1-phenyl-2-pyrazolin-5-one (hereinafter referred at "EDV") in 8 parts of N-methyl-2-pyrrolodone and 2 parts of crotamiton. Liquid B and liquid C were added to liquid A. Also, 2.5 parts of methyl acrylate/acrylic acid 2-ethylhexyl copolymer resin emulsion and 0.1 part of aluminum hydroxide gel were added and mixed homogeneously to obtain a mixture (Preparation A) for adhesive preparation.

(1)-(b) Koide et al.

In addition, according to the procedure of Example 3 of Koide et al. (JP 10-265373) in which the adhesive preparation showing the highest adhesion in 30 preparations of Examples is disclosed, a mixture (Preparation B) for an adhesive preparation was prepared as follows. That is, the following components were kneaded for 30 minutes:

| | |
|---|---|
| - EDV | 3.0 parts |
| - Polyacrylic acide (average molecular weight: 150,000) | 4 parts |
| - Sodium polyacrylate | 1.5 parts |
| - Polyvinyl alcohol | 1.0 part |
| - Glycerin | 15 parts |
| - Sorbitol | 10.0 parts |
| - Glycine | 0.1 part |
| - Synthetic hydrotalcite | 0.05 part |
| - Magnesium metasilicate aluminate | 0.1 part |

| | |
|---|---|
| - Polyoxyethylene glycol ether | 1.0 part |
| - Kaolin | 6.0 parts |
| - Nikkol MYL-10 | 1.5 parts |
| - Castor oil | 1.0 part |
| - Propylene glycol | 3.0 prts |
| - 1,3-Butylene glycol | 3.0 parts |
| - Pure water | 49.75 parts. |

In addition, another mixture (Preparation C) was prepared similarly to the preparation of Preparation B except that 52.75 parts of pure water was used instead of 3 parts of EDV and 49.75 parts of pure water. That is, Preparation C contained no EDV being an active ingredient.

(1)-(c) Mori et al.

According to the procedure of Example 3 of Mori et al. (EP 1174132), a mixture (Preparation D) for an absorption preparation was prepared and an absorption preparation was prepared from the mixture as follows:

3 parts of EDV (in place of the active ingredient of Mori et al.) were dissolved in 150.0 parts of isoprapanol as the solvent, and then 10.0 parts of N-vinyl acetamide copolymer (PNVA GE167, a product of Showa Denko K.K.), 1.5 parts of aluminum gel GLYCINAL, 0.5 part of tartaric acid, 5.0 parts of methyl cellulose and 10.0 parts of polyacrylic acid solution were mixed by stirring. The mixture solution containing 39.0 parts of glycerin, 10.0 parts of propylene glycol and 21.0 parts of water were added and continuously stirred to obtain Preparation D. The solvent-type plaster with the desirable viscosity for the plaster is spread

out over the non-woven fabric, then solvent is removed by heat drying and the strippable film made of polyester was adhered.

Further, a mixture (Preparation E) for adhesive preparation was obtained according to the procedure for obtaining Preparation D except that EDV was not added.

In addition, according to the procedure of Example 4 of Mori et al. (EP 1174132), a mixture (Preparation F) for an absorption preparation was prepared and an absorption preparation was prepared from the mixture as follows:

3 parts of EDV (in place of the active ingredient of Mori et al.) were dissolved in 33.4 parts of water, and then 1.0 part of tartaric acid, 10.0 parts of polyacrylic acid solution and 10.0 parts of acrylric acid ester copolymer emulsion were added and stir-mixed. The mixture solution containing 6.0 parts of N-vinyl acetamide copolymer (PNVA GE167, a product of Showa Denko K.K.) and 8.0 parts of polyethylene glycol prepared in advance, and the mixture solution containing18.0 parts of glycerin, 5.0 parts of methyl cellulose and 5.0 parts of white carbon (hydrous silicon dioxide) were added and continuously stirred. Next, 0.3 part of polyoxyethylene laurylether and 2.0 parts oleyl alcohol were added and mixed to obtain Preparation F. Finally, 0.3 part of dried alluminum hydroxide gel and 2.0 parts of water were added and mixed. The plaster (Preparation F) thus obtained was spread out over the non-woven fabric and the strippable film made of polyester was adhered.

Further, also in this case, a mixture (Preparation G) for adhesive preparation was obtained according to the procedure for obtaining Preparation F except that EDV was not added.

(2) Formability, Adhesiveness and Skin Transmission Property

Preparation A was spread on a polyester non-woven fabric, and then covered with a polyethylene film. This was then cut into predetermined dimensions to obtain an adhesive

preparation. This adhesive preparation was easily prepared, and adhesiveness between Preparation A and the non-woven fabric (a support) was good. The adhesive preparation was subjected to "in vitro skin transmission test" stated in the specification, and the transmission property ($AUC_{0\text{-}24h}$) was 4908.11 ± 641.35 ng·h/ml showing that it has a sufficiently high skin transmission property.

On the other hand, Preparations B and C were soft and in the form of liquid having flowability. Preparation B or C was spread on a polyester non-woven fabric, and then covered with a polyethylene film. This was then cut into predetermined dimensions to obtain an adhesive preparation. The solvent exuded in the support. Adhesiveness between Preparation B or C and the non-woven fabric (a support) was weak and thus the preparation on the support was left on the skin. The adhesive preparation prepared from Preparation B was subjected to "in vitro skin transmission test" stated in the specification, and the transmission property ($AUC_{0\text{-}24h}$) was 3366.58 ± 1239.01 ng·h/ml that was inferior to that of Preparation A.

Preparations D and E were hard, and thus difficult to be spread over the support. In addition, these preparations were colored in yellow-brown and 20-30% of the components therein were lost, due to heat drying. Adhesiveness between Preparation D or E and the non-woven fabric (a support) was weak. The adhesive preparation prepared from Preparation D was subjected to "in vitro skin transmission test" stated in the specification, and the transmission property ($AUC_{0\text{-}24h}$) was 1588.56 ng·h/ml that was extremely inferior to that of Preparation A.

Preparations F and G were hard. Adhesiveness between Preparation F or G and the non-woven fabric (a support) was weak and thus the adhesive preparation was apt to be

removed from the skin. The adhesive preparation prepared from Preparation F was subjected to "in vitro skin transmission test" stated in the specification, and the transmission property ($AUC_{0\text{-}24h}$) was 3850.23 ng·h/ml that was inferior to that of Preparation A.

The results of the Formability, Adhesiveness and Skin Transmission Property Tests are summarized below in Table 1.

**Table 1**
**Results of the Formability, Adhesiveness and Skin Transmission Property Tests**

| Preparation | Reference | Summary of Results |
|---|---|---|
| A | Specification, Example 1 | 1. Demonstrated good adhesiveness between Preparation A and the non-woven fabric (support).<br>2. After being subjected to an "in vitro skin transmission test[1]," the transmission property ($AUC_{0\text{-}24h}$) was 4908.11 ± 641.35 ng·h/ml. |
| B | Koide, Example 3 | 1. Both Preparation B and C demonstrated weak adhesiveness to the non-woven fabric (a support) and thus the preparation on the support was left on the skin.<br>2. After being subjected to an "in vitro skin transmission test," the transmission property ($AUC_{0\text{-}24h}$) was 3366.58 ± 1239.01 ng·h/ml.<br>a. **The transmission property of Preparations B and C is approximately 31.4% less than Preparation A.** |
| C | Similar to Preparation B, except that 52.75 parts of pure $H_2O$ were used instead of 3 parts EDV and 49.75 parts of pure $H_2O$ | |
| D | Mori, Example 3 | 1. Preparations D and E were hard and difficult to spread over the support.<br>2. Both Preparations D and W were yellow-brown in color and 20-30% of the components therein were lost, due to heat drying and demonstrated weak adhesiveness to the non-woven fabric (a support).<br>3. After being subjected to an "in vitro skin transmission test," the transmission property ($AUC_{0\text{-}24h}$) was 1588.56 ng·h/ml<br>a. **The transmission property of Preparations D and E is approximately 67.6% less than Preparation A.** |
| E | Similar to Preparation D, except that no EDV was added | |
| F | Mori, Example 4 | 1. Preparations F and G were hard and difficult to spread over the support.<br>2. Both Preparations F and G demonstrated weak adhesiveness to the non-woven fabric (a support) and thus the adhesive preparation was apt to be removed from the skin.<br>3. After being subjected to an "in vitro skin transmission test," the transmission property ($AUC_{0\text{-}24h}$) was 3850.23 ng·h/ml<br>a. **The transmission property of Preparations F and G is approximately 21.5% less than Preparation A.** |
| G | Similar to Preparation F, except that no EDV was added | |

[1] Note: the methodology of the "in vitro skin transmission test" can be found in paragraph [0042] of the specification.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: Mar. 01. 2010. Jun MORI

Jun MORI